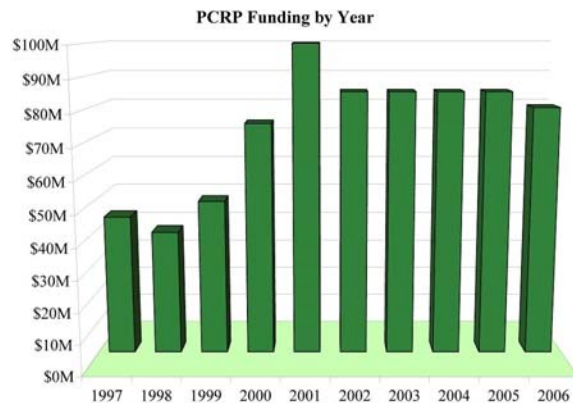


# Congressionally Directed Medical Research Programs Prostate Cancer Research Program (PCRP)

## Introduction to the PCRP

Grassroots efforts by the prostate cancer advocacy community led to congressional appropriations to the Department of Defense (DOD) of \$45 million (M) in Fiscal Year 1997 (FY97) for prostate cancer research. Since then, a total of \$730M has been appropriated, including \$80M for FY06. This funding energized the



development of a unique partnership among the public, Congress, and the military. The Congressionally Directed Medical Research Programs (CDMRP), within the U.S. Army Medical Research and Materiel Command (USAMRMC), manages the PCRP. The PCRP review of proposals is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine; this model has received high praise from scientists, advocates, and Congress. Enthusiasm for the program has skyrocketed among researchers; the number of proposal submissions for FY06 is expected to double

that of the inaugural year. Today, the PCRP is the second leading source of extramural prostate cancer research funding in the United States.

The goal of the PCRP is to fill important gaps in support of prostate cancer research not addressed by other funding agencies. The program focus is adapted yearly to facilitate rapid change and to better target funding to the most critical research areas.

## Vision of the PCRP

The overall goal of the PCRP is to conquer prostate cancer. To accomplish this goal, the PCRP mission is to support innovative and multidisciplinary research. The PCRP is particularly interested in finding and funding innovative, high-impact research that seeks to (1) prevent prostate cancer, (2) detect prostate cancer, (3) cure prostate cancer, and (4) improve the quality of life for individuals living with prostate cancer and for their families.

## Unique Features of the PCRP

### Consumer Advocate Participation

Consumer advocates actively participate in setting program priorities and making funding decisions. More than 150 consumer advocates have served on peer and programmatic review panels for the PCRP. Their firsthand experience with prostate cancer provides a unique perspective that helps the scientists understand the human side of the disease and allows for funding decisions that reflect the concerns and needs of patients, their families, and clinicians. Consumer advocates also share what they have learned with their communities, resulting in increased awareness of the importance of research and a stronger relationship between the scientific community and the consumer advocate community. The overwhelming success of the PCRP inclusion of consumer advocates in the review process has influenced other funding agencies to follow this precedent.



*"The U.S. Army's CDMRP is one of the best examples of direct action that is specifically dedicated to targeting prostate cancer and eliminating its tragic consequences ... the CDMRP is highly respected and is the example that other research programs should be modeled after. It was an honor to serve on the Integration Panel and to have the final review of, and vote for, the very best therapies specifically targeted against prostate cancer."*

John Willey, Consumer Programmatic Reviewer, PCRP

## Program Focuses

To fill important research gaps, the PCRP has focused on four broad areas:

- **Impacting Patients' Lives:** bringing new discoveries to patients through clinical research and trials
- **Eliminating Health Disparity:** eliminating the disparate burden of prostate cancer on the African-American community and other affected populations
- **Exploring Innovative, Groundbreaking Ideas and Technology:** funding high-risk and high-gain research of exciting new ideas
- **Training the Next Generation of Researchers:** inspiring and training prostate cancer researchers during their early career stages

## Research Funding Strategy of the PCRP

The PCRP has implemented research and training award mechanisms that are specifically aimed at filling critical gaps and moving the field of prostate cancer research closer to finding a cure.

AWARD MECHANISM	FOCUS
• <b>Clinical Consortium Award:</b> provides resources to facilitate the rapid execution of <i>collaborative</i> Phase II or Phase II-linked Phase I clinical studies	Impact
• <b>Clinical Trial Award:</b> funds the rapid execution of novel Phase I, Phase I/II, or Phase II clinical trials	Impact
• <b>Collaborative Undergraduate HBCU Student Summer Training Program Award:</b> provides educational and training opportunities in prostate cancer research for undergraduate students at Historically Black Colleges and Universities (HBCU)	Training
• <b>Consortium Award:</b> funds major, coordinated goal- or product-driven research effort that is multi-institutional and national in scope and addresses overarching themes	Disparity & Impact
• <b>Exploration—Hypothesis Development Award:</b> supports initial exploration of untested, potentially groundbreaking concepts in prostate cancer	Innovation
• <b>HBCU Collaborative Partnership Award:</b> fosters collaborations between an HBCU and another institution that establish sustained HBCU prostate cancer research and training programs focused on disparity	Disparity & Training
• <b>Health Disparity Research Award:</b> supports research on the disparate burden of prostate cancer within affected populations and communities	Disparity
• <b>Health Disparity Training Award:</b> provides training opportunities to researchers early in their careers to study the disparate burden of prostate cancer within affected populations and communities	Disparity & Training
• <b>Idea Development Award:</b> supports innovative ideas and technology across all areas of laboratory, clinical, behavioral, and epidemiological research, including clinical trials	Innovation
• <b>New Investigator Award:</b> funds innovative research from newly independent investigators working in collaboration with experienced prostate cancer researchers	Innovation & Training
• <b>Physician Research Training Award:</b> prepares physicians for careers in prostate cancer research through a mentored training experience in a laboratory or clinical setting	Impact & Training
• <b>Prostate Cancer Training Award:</b> provides prostate cancer research training opportunities to individuals early in their careers	Training

---

## Success Stories

### Impacting Patients' Lives

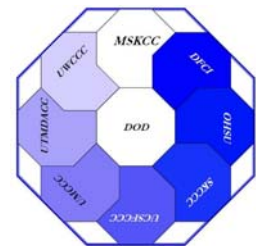
**Consortium Award.** Dr. Jonathan Simons of Emory University leads a multi-institutional effort to define the lethal phenotype of prostate cancer. Since prostate cancer becomes incurable when it metastasizes to bone, Dr. Simons' group is focusing on the biology of bone metastasis, an innovative molecular classification system for diagnosis, and new therapeutics. Dr. Simons' group is working with industry to place three new therapeutics in clinical trials.



**Clinical Consortium Award.** The Clinical Consortium Award supports the creation of a major multi-institutional clinical trial resource to facilitate rapid execution of novel clinical trials. The goal is to speed development of novel therapeutics that will ultimately decrease the impact of the disease. Dr. Howard Scher, Chief Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, leads this multi-institutional consortium.



*Participating clinical sites and lead investigators are: Dr. Tomasz Beer, Oregon Health and Science University; Dr. Michael Carducci, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University; Dr. Maha Hussain, University of Michigan Comprehensive Cancer Center; Dr. Philip Kantoff, Dana-Farber Cancer Institute; Dr. Christopher Logothetis, The University of Texas M. D. Anderson Cancer Center; Dr. Eric Small, University of California, San Francisco Comprehensive Cancer Center; and Dr. George Wilding, University of Wisconsin, Comprehensive Cancer Center.*



**Clinical Trial Award.** The Clinical Trial Award funds novel Phase I and Phase II clinical trials expected to impact prostate cancer significantly. One promising clinical trial is being conducted by Dr. Robert DiPaola of the University of Medicine and Dentistry of New Jersey. Dr. DiPaola's research team found that combining two factors, 13-cis retinoic acid and alpha-interferon, decreased levels of the survival factor BCL-2 in cell lines, and then hypothesized that these two factors would enhance the effectiveness of conventional chemotherapy. Dr. DiPaola and colleagues combined retinoic acid and interferon with taxotere and estramustine (R.I.T.E.) in a successful Phase I study with patients with hormone-refractory prostate cancer. Phase II trials of R.I.T.E are under way.



### Eliminating Health Disparity

**Consortium Award.** Dr. James Mohler of the Roswell Park Cancer Institute leads a multi-institutional effort (including the University of North Carolina and Louisiana State University) to determine why African-American men have more than twice the mortality rate from prostate cancer than Caucasian-American men. Interestingly, there is also a geographic disparity within the African-American population; African Americans in North Carolina have one of the highest, and African Americans in Louisiana have one of the lowest, mortality rates from prostate cancer in the United States. This large comprehensive study will provide evidence on whether health disparities in prostate cancer are due to (1) interaction with the health care system, (2) diet and biology, and/or (3) characteristics of the tumor.



### Health Disparity Training Award.

**Genetic Risk Factors.** Dr. Matthew Freedman, while working at Massachusetts General Hospital, identified risk factors for prostate cancer in African Americans using large-scale genomic approaches. In the largest study of this type to date, his research team found no association between genetic variants of the androgen receptor gene and prostate cancer risk among African Americans, Native Hawaiians, Japanese, Latinos, and Caucasians. However, they did find



---

two gene variants of IGF-1 that were strongly associated with prostate cancer risk across all ethnic groups. Dr. Freedman, now at the Dana-Farber Cancer Institute, is testing over 1,000 gene markers in an African-American population to identify gene variants that contribute to increased risk of prostate cancer, thereby leading to more effective screening, prevention, and treatment strategies.

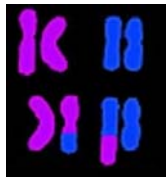
### **HBCU Collaborative Partnership Award.**

The goal of this partnership between Florida A&M University (FAMU) and the Moffitt Cancer Center (MCC) is for FAMU to create "The FAMU Minority Prostate Cancer Training and Research (FAMU MPC) Center." After FAMU researchers, led by Dr. Folakemi Odedina, received mentoring and training from MCC scientists led by Dr. Nagalakshmi Kumar, the FAMU and MCC scientists collaborated on studies focused on health disparity and prostate cancer. Studies to develop community outreach and education programs have been highly successful. Products include kiosks in drug stores, consumer forums, online training modules, and television programs.

## **Exploring Innovative, Groundbreaking Ideas and Technology**

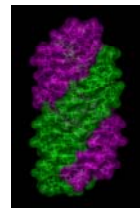
### **Idea Development Award.**

**Discovery of Gene Fusions.** Dr. Arul Chinnaiyan of the University of Michigan discovered that gene fusions play a widespread role in the development of prostate cancer. Gene fusions, the accidental joining of the DNA in two genes, are commonly found in blood cancers but only rarely in solid tumors. Dr. Chinnaiyan's team found recurrent gene fusions between the prostate-specific androgen-regulated gene *TMPRSS2* and *ERG* or *ETV1* (two genes linked to leukemias) in approximately 80% of the prostate cancer tissue samples analyzed. These findings have broad implications for prostate cancer diagnosis and treatment, as the fused genes may provide both a novel biomarker and a therapeutic target in the majority of prostate cancers. Furthermore, these findings suggest a new model for cancer research: chromosomal rearrangements can occur in epithelial cancers.



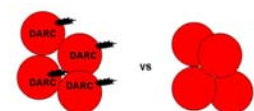
### **New Investigator Awards.**

**Finding NEMO: A New Type of Cancer Therapy.** Dr. Paula Bates and her colleagues at the University of Louisville discovered a class of synthetic molecules, called guanine-rich oligonucleotides (GROs), with a natural affinity for a protein (nucleolin) on the surface of cancer cells. After attaching to a tumor cell, GROs are drawn inside and trigger its death. This mechanism is different from any cancer therapy discovered thus far. Inside the cell, GROs target several proteins, including NEMO, a survival factor that helps cells become resistant to chemotherapy. A specific GRO (AGRO100/AS1411) showed promising antitumor activity with few adverse side effects in a recently conducted Phase I clinical trial.



**Laser Technology to Improve Quality of Life.** Urethral and bladder neck strictures (narrowing) occur as a consequence of prostate cancer surgery and result in urinary incontinence. In an effort to reduce scarring and recurrence of strictures, Professor Nathaniel Fried of Johns Hopkins University recently used a new laser technology (used in cosmetic wrinkle removal) to precisely incise the urethra and bladder neck during preclinical studies. Dr. Fried's laboratory showed that the Erbium:YAG laser is up to 30 times more precise than other lasers used in urology. These findings hold great promise for increasing the quality of life of thousands of men after prostate cancer surgery.

**A New Genetic Link to Prostate Cancer in African Americans.** Dr. Alex Lentsch of the University of Cincinnati College of Medicine suspected that there may be a link between the lack of a protein called DARC on red blood cells and the greater incidence and mortality of prostate cancer in the African-American



---

population. The absence of DARC on red blood cells is a genetic mechanism of protection against malaria. Approximately 70% of African Americans are missing DARC on their red blood cells. Dr. Lentsch's team found that red blood cells from DARC-deficient mice were unable to inhibit prostate tumor growth. Thus, the absence of DARC protein, which occurs in the majority of African Americans, may be a contributing factor to the increased mortality from prostate cancer in this population.

#### Exploration Hypothesis Development Awards.

**Citrus Flavonoids and Prevention of Prostate Cancer.** Dr. Susanne Henning of University of California, Los Angeles (UCLA) tested her hypothesis that nutrients in grapefruit and oranges called flavonoids have important biological functions besides their known effects as antioxidants. Dr. Henning and colleagues discovered that a particular citrus flavonoid called naringenin could stimulate DNA repair in prostate cancer cells. These data suggest that citrus fruits may have cancer-preventive effects that result from the prevention of gene mutations caused by environmental factors.



#### Training the Next Generation of Researchers

##### Prostate Cancer Training Awards.

**Imaging.** Dr. Baowei Fei of Case Western Reserve University envisions using imaging to create “before and after” treatment snapshots of the prostate to improve prostate cancer diagnosis and therapy. Dr. Fei's approach is to integrate structural and anatomical details with real-time, functional data from two or more different imaging techniques. Dr. Fei created novel image registration techniques that combine multiple imaging modalities for early detection and image-guided therapies for prostate cancer. These novel techniques could improve dosage planning for both external beam and brachytherapy treatments of prostate cancer.



**New Blood Test.** Dr. Xiaoju Wang and Dr. Arun Sreekumar of the University of Michigan developed a new blood test that is more accurate than the PSA test. This test is based on a panel of 22 biomarkers that together are more accurate than a single marker like PSA. These biomarkers generated false alarms only 12% of the time (compared to 80% for PSA). Importantly, the test was able to accurately identify prostate cancer in samples with intermediate PSA scores (2.5 to 10 ng/mL). This new prostate cancer test could potentially be used in combination with PSA screening and offers the hope of earlier and more accurate diagnosis.



**Selenium-Induced Biomarkers.** Dr. Yan Dong of the Roswell Park Cancer Institute identified a panel of biomarkers that respond to selenium. Selenium is a trace mineral found in seafood, grains, and vegetables that helps prevent cancer by protecting against the damaging effects of free radicals, boosting the immune system, and inhibiting tumor angiogenesis. Clinical trials testing selenium chemoprevention of prostate cancer are under way, and selenium-responsive biomarkers are needed to measure the effectiveness of selenium in these trials. Dr. Dong's team identified several candidate selenium-responsive biomarkers that provide exciting clues about selenium action and are potential diagnostic markers and therapeutic targets.

##### Physician Research Training Award.

**Discovery of New Pathways in Hormone-Refractory Prostate Cancer.** Dr. Ingo Mellinghoff of UCLA dissected signaling pathways that modulate function of the androgen receptor. He found the surprising results that a signaling pathway called the HER2/ERBB3 kinase pathway (and not the expected EGFR pathway) modulates androgen receptor function. These findings have clinical implication as they suggest that in hormone-refractory tumors the HER2/ERBB3 kinase pathway is a critical target for kinase inhibitor therapy.



---

## Collaborative Undergraduate HBCU Student Summer Training Program Award.

Dr. Timothy McDonnell of The University of Texas M. D. Anderson Cancer Center and Dr. Debabrata Ghosh of Texas Southern University (TSU) lead a unique scientific training program with the ambitious goals of increasing the number of individuals with comprehensive training in prostate cancer and increasing the number of individuals from underrepresented populations in the scientific workforce. Undergraduate science majors from TSU attend courses and presentations at TSU and M. D. Anderson, perform intensive summer laboratory research at M. D. Anderson, present their work at local and national meetings, and receive follow-up training, mentoring, and career guidance.

## Summary of PCRP Research Highlights

**Basic Research.** Basic research discoveries are critical in the fight against prostate cancer because they provide the foundation for the development of new diagnostic and therapeutic tools.

- Determining causes of health disparity and prostate cancer in African Americans (Dr. James Mohler)
- Discovery of the first gene fusions in prostate cancer (Dr. Arul Chinnaiyan)
- Discovery of biological functions in cancer of DARC (a protein implicated in health disparity of prostate cancer) (Dr. Alex Lentsch)
- Discovery of a signaling pathway that modulates androgen function (Dr. Ingo Mellinghoff)



**Prevention.** One approach to fighting prostate cancer is to prevent the disease from occurring and decrease incidence rates.

- Discovery of mechanisms by which citrus flavonoids prevent prostate cancer (Dr. Susanne Henning)
- Identification of a panel of biomarkers that are responsive to selenium (Dr. Yan Dong)

**Detection and Diagnosis.** Men with early-stage prostate cancers have an excellent prognosis. Therefore, early detection and diagnosis of prostate cancer could greatly improve survival.

- Discovery of IGF-1 gene variants related to increased risk of prostate cancer (Dr. Matthew Freedman)
- Development of a new 22-biomarker blood test that is more accurate than the PSA test (Dr. Xiaojun Wang and Dr. Arun Sreekumar)

**Treatment and Quality of Life.** Once patients are diagnosed with prostate cancer, it is critical to provide effective treatments against the cancer and maintain a high quality of life.

- Creating an infrastructure to expedite multi-institutional clinical trials (Dr. Howard Scher)
- Developing new clinical therapeutics for late-stage prostate cancer (Dr. Jonathan Simons)
- Performing Phase I and II clinical trials of R.I.T.E. (Dr. Robert DiPaola)
- Discovery of a new class of cancer therapies called GROs (Dr. Paula Bates)
- Using laser therapy to reduce urinary incontinence (Dr. Nathaniel Fried)
- Development of new imaging techniques to guide therapies (Dr. Baowei Fei)



**<http://cdmrp.army.mil/pcrp>**

**<http://cdmrp.army.mil>**